Disclosure from WW Yew

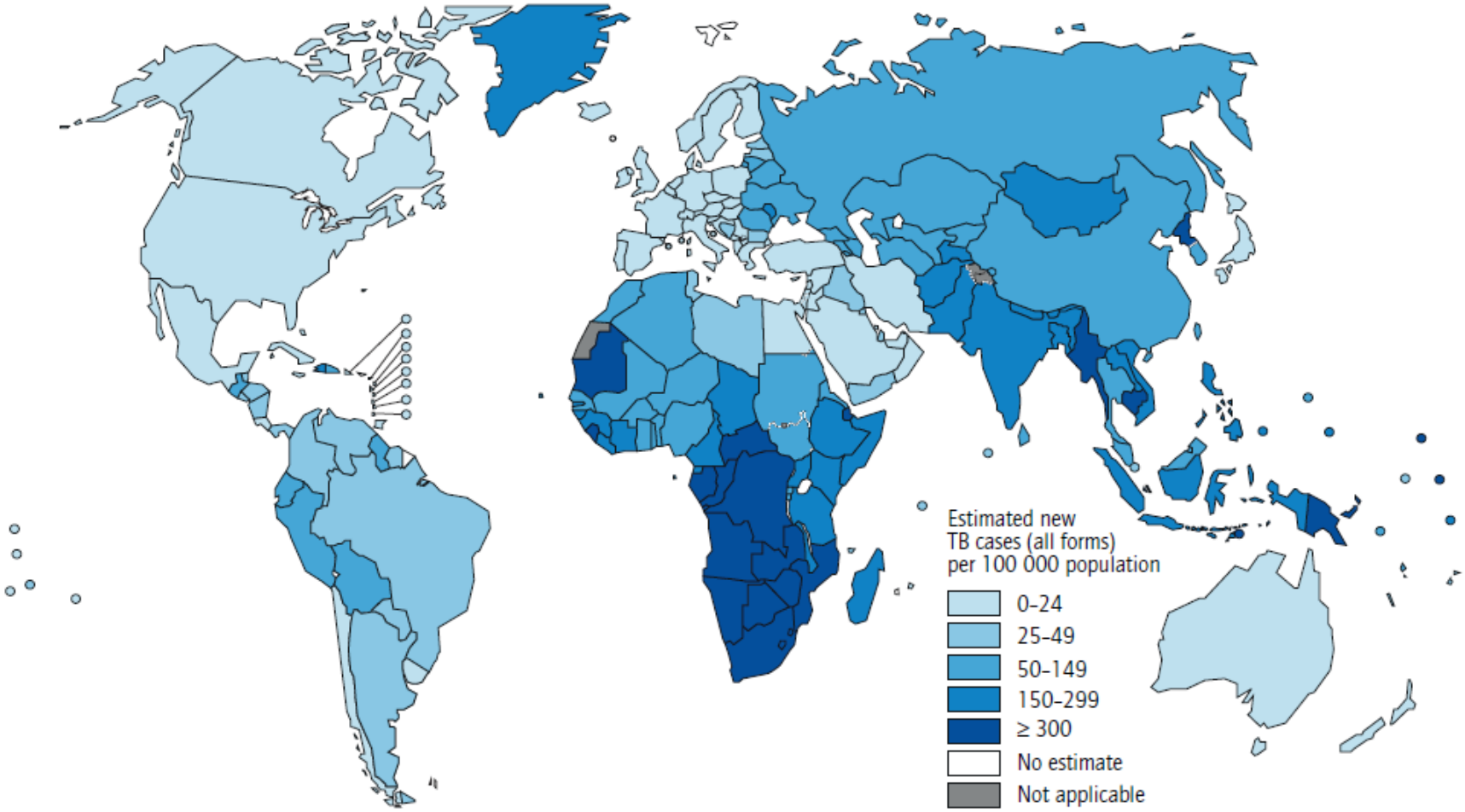
- **Aside from my University affiliations, I am also consultant to Otsuka Pharmaceutical Co that produces the new TB drug named delamanid**

NEW STRATEGIES
in the
TREATMENT OF TUBERCULOSIS
Promise and Limitation?

Dr Stanley Ho Medical Foundation
Annual Scientific Meeting
January 2015

WW Yew
香港中文大學
The Chinese University of Hong Kong

FIGURE 2.5 **Estimated TB incidence rates, 2011**

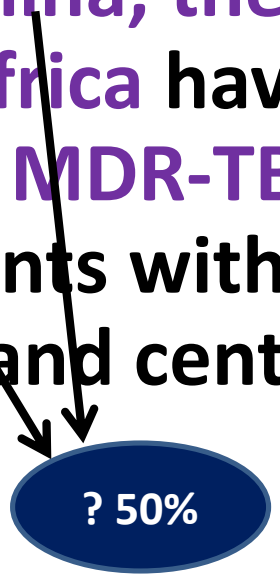


- **Multidrug-Resistant or MDR-TB (with bacillary resistance to at least to Rifampicin and Isoniazid)**

- **Extensively Drug-Resistant TB: MDR-TB with additonal bacillary resistance to Fluoroquinolone(s) and at least one of the three Second-line Injectables, viz Kanamycin, Amikacin and Capreomycin.**

WHO Global TB Report 2013

- Worldwide, 3.7% of new cases and 20% of previously treated cases were estimated to have MDR-TB. The average proportion of XDR-TB among MDR-TB cases was 9.0%
- India, China, the Russian Federation, and South Africa have almost 60% of the world's cases of MDR-TB. The highest proportions of TB patients with MDR-TB are in eastern Europe and central Asia.



Yew WW et al
Emerging Drugs for the Treatment of TB
Expert Opin Emerg Drugs 2011

There clearly emerges a *pressing need to develop*

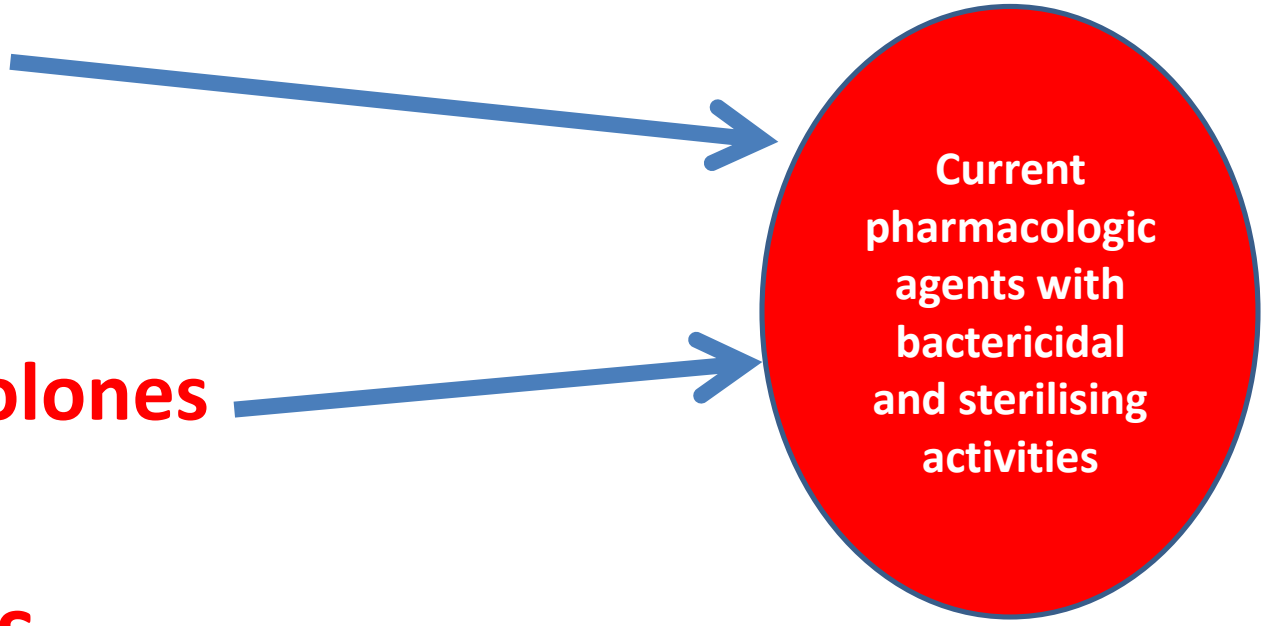
New Strategies for

- **Shortening and simplifying treatment of drug-susceptible TB**

TO LESSEN THE RISK OF DEVELOPMENT OF MDR-TB

Potential Candidates for Reducing 6-Month Treatment of TB

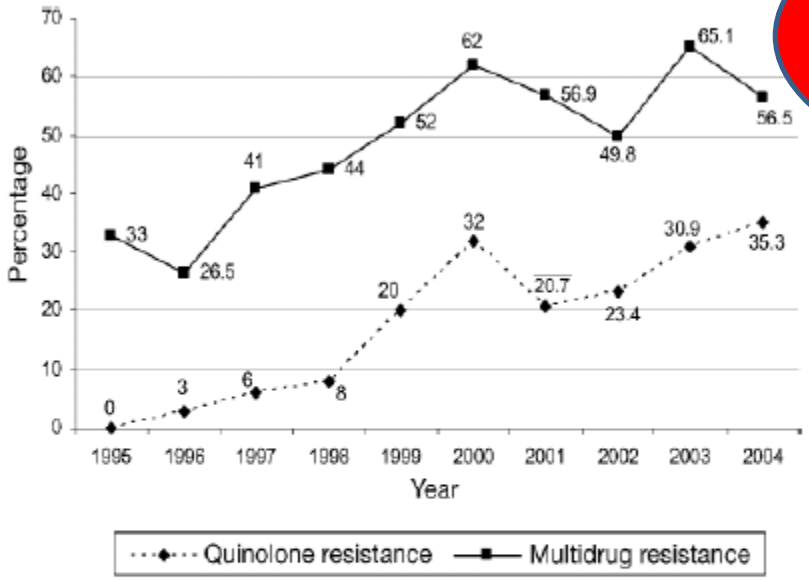
- **Rifamycins**
- **High-Dose**
- **Fluoroquinolones**
- **NEW DRUGS**



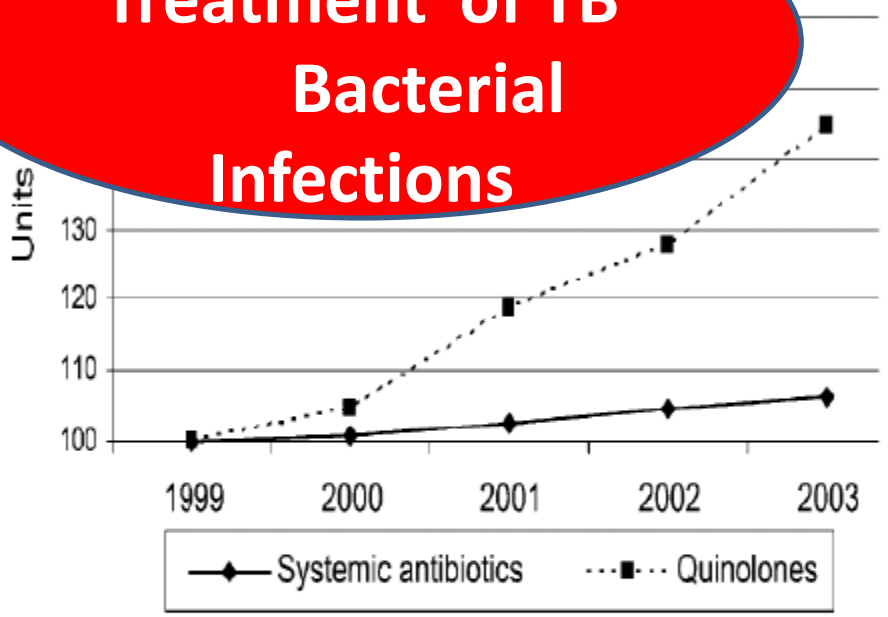
Issues of Paramount Importance for Shortened Regimens for Drug-Susceptible TB

- **Optimal Dosage and Scheduling for**
- **desired efficacy**
- **guaranteed tolerability /safety**

Increasing Fluoroquinolone Resistance in MTB in India (Mumbai)



Suboptimal Treatment of TB Bacterial Infections



Agrawal D, et al. Int J Tuberc Lung Dis 2009;13:79-83

International Union Against Tuberculosis and Lung Disease

Another direction of New Strategies in Treatment of TB

Harnessing Current Tools for Treatment of MDR-TB and XDR-TB

- **Optimizing Use of Later-Generation Fluoroquinolones**

- **Evaluating Use of Repurposed Drugs (WHO Group 5 Agents)**

Yew WW et al Comparative Roles of Levofloxacin & Ofloxacin in Treatment of MDR-TB Chest (2003)

- The success rates for the LEVOFLOXACIN group were 90.0% (overall), 96.2% (ofloxacin-susceptible cases), and 78.6% (ofloxacin-resistant cases), in comparison with 79.7% (overall), 87.5% (ofloxacin-susceptible cases) and 45.5% (ofloxacin-resistant cases) for the OFLOXACIN group.

From 20 months

Van Deun A, et al
Short, Highly Effective and Inexpensive Standardized Treatment of Multidrug-Resistant Tuberculosis [2]
Am J Respir Crit Care Med (2010)

- **The final most effective regimen required a minimum of 9 months duration with HIGH-DOSE GATIFLOXACIN, Clofazimine, Ethambutol and Pyrazinamide throughout, supplemented by Prothionamide, Kanamycin and High-Dose Isoniazid during an intensive phase of a minimum of 4 months, giving a relapse-free CURE of 87.9% (95% CI 82.7 – 91.6%) among 206 patients**

Not all apples taste the same!

STREAM TRIAL
High-dose
Moxifloxacin

Opti-Q Trial
High-dose
Levofloxacin

SAFETY

Dooley KE et al JID 2013

- …..**Clofazimine** may contribute to new short-course DR-TB regimens. **Beta-lactams** merit further evaluation…… **Linezolid** appears effective …….Thiacetazone is too toxic to merit further evaluation. Mycobacterium tuberculosis has intrinsic inducible resistance to clarithromcycin……

Cox H & Ford N Linezolid for the Treatment of complicated Drug-Resistant TB: A Systematic Review and Meta-Analysis (1) IJTLD 2012

- **A total of 11 studies with 148 patients**
- **The pooled proportion for treatment success was 67.99% (95%CI 58.00-78.99)**
- **There was no significant differences in success comparing daily linezolid dose (=< 600 vs > 600 mg) and mean linezolid duration (=< 7 vs > 7 months).**
  The pooled estimate for the frequency of any adverse events was 61.48% (95%CI 40.15-82.80), **with 36.23% (95% CI 20.67-51.79), discontinuing linezolid due to adverse events.**

Cox H & Ford N Linezolid for the Treatment of complicated Drug-Resistant TB: A Systematic Review and Meta-Analysis (2) IJTLD 2012

- **Treatment success with linezolid was equal to or better than that commonly achieved for uncomplicated drug-resistant TB, better than previous reports for previously treated patients and those with XDR-TB. While data are limited, LINEZOLID appears be a useful drug, albeit associated with significant adverse events, and should be considered in the treatment of complicated drug-resistant TB**

Koh WJ et al Daily 300 mg Dose of Linezolid for MDR-TB and XDR-TB. Updated Analysis of 51 Patients JAC 2012

- **Patients were treated with linezolid for a median of 413 days.**
- **Favourable outcome (success or on treatment after conversion) in 40 (78%)**
- **Median time of culture conversion: 55 days**
- **27% patients discontinued treatment due to neurotoxicity**

Chang KC, Yew WW, Cheung SW et al

- **Can Intermittent Dosing Optimize Prolonged Linezolid Treatment of Difficult MDR-TB?**
- **Antimcrob Agents Chemother 2013; 57: 3445- 3449**

Dey T et al Outcomes of Clofazimine for the Treatment of Drug-Resistant TB: A Systematic Review and Meta-Analysis JAC 2012

The available evidence suggests that CLOFAZIMINE could be considered as an additonal therapeutic option in the treatment of DR-TB. The optimal dose of clofazimine and duration of use require further investigation

Grosset JH et al Assessment of Clofazimine Activity in a Second-Line Regimen for TB in Mice AJRCCM 2013

- Moxifloxacin, EMB, PZA, Amikacin +/- Clofazimine
- After 2 months. The bacillary load in lungs was reduced from 9.74 log10 at baseline to 3.61 and 4.68 in mice treated with or without Clofazimine, respectively ($P<0.001$).
- Mice treated with Clofazimine were culture-negative after 5 months, whereas those not treated remained culture-positive for the entire 9 months of study. The relapse rate was 7% among mice treated with 8-9 months of Clofazimine

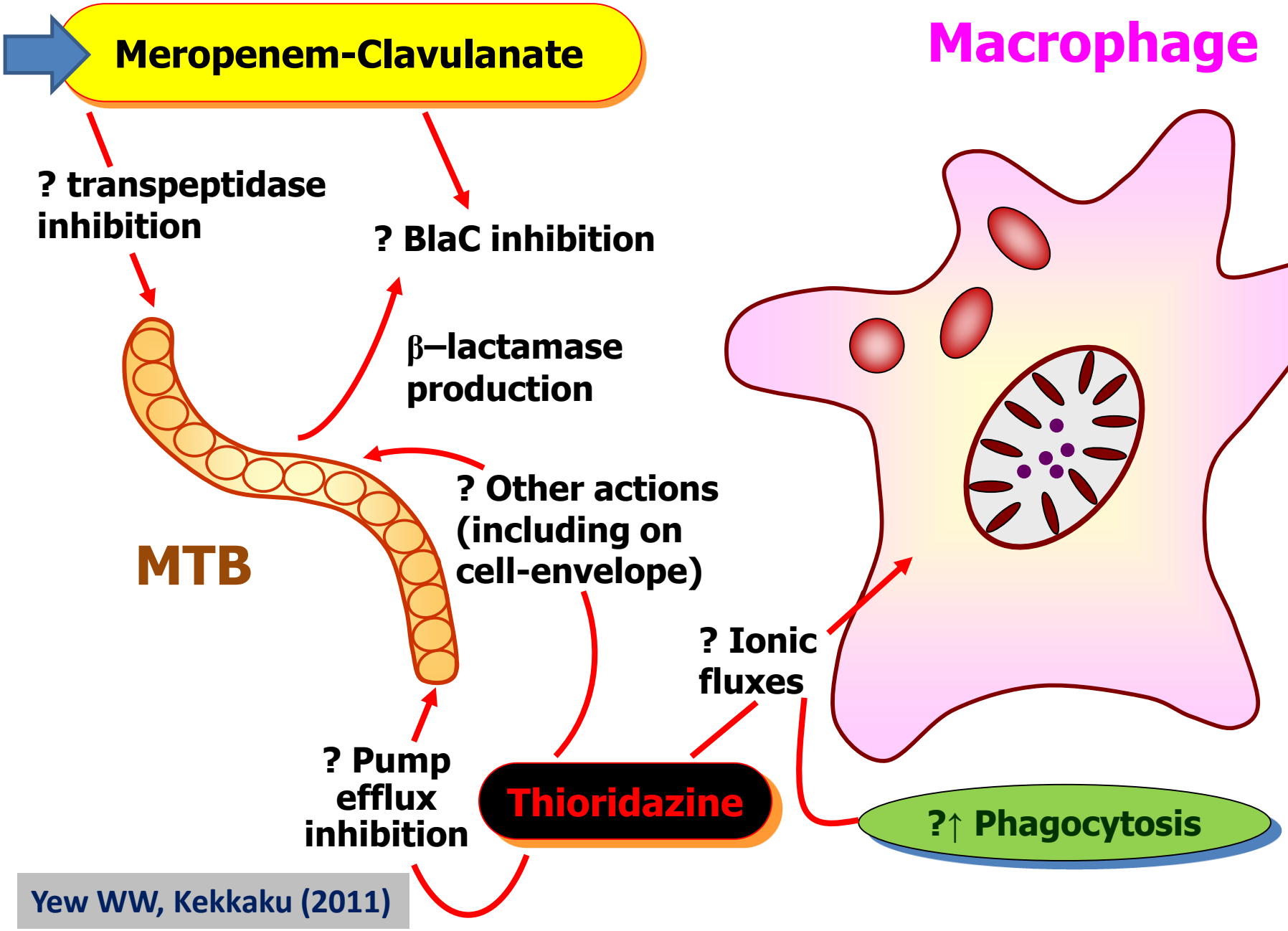
- **Padayatchi N et al Clofazimine in the Treatment of XDR-TB with HIV Coinfection in South Africa: A Retrospective Cohort Study J Antimicrob Chemother 2014**
- **Clofazimine addition was associated with improved culture conversion (40% vs 28.6%)**
- **The hazard rate ratio of 6-mo culture conversion of regimens containing clofazimine vs those with no clofazimine was 2.54**
- **Adverse reactions were largely minor**

Hartkoom RC et al Cross-Resistance between Clofazimine and Bedaquiline through Up-Regulation of MmpL5 in MTB Antimicrob Agents Chemother 2014

- **To understand better resistance mechanisms, clofazimine-resistant mutants of Mtb were isolated in vitro, and, unexpectedly found to have cross-resistance to bedaquiline. Mutations in the transcriptional regulator Rv0678, with concurrent upregulation of the multisubstrate efflux pump MmpL5, were accountable. These findings may have therapeutic implications.**

Andries K et al Acquired Resistance of MTB to Bedaquiline PLoS One 2014

- **Resistance to bedaquiline (BDQ) and cross-resistance to clofazimine (CFZ) was found to be due to mutations in Rv0678, a transcriptional repressor of the genes encoding the MmpS5-MmpL5 efflux pump.**
- **Efflux-based resistance was detected in paired isolates from patients treated with BDQ, in whom it was confirmed to decrease bactericidal efficay.**
- **The cross-resistance between BDQ and CFZ may have important clinical implications**



Yew WW, Kekkaku (2011)

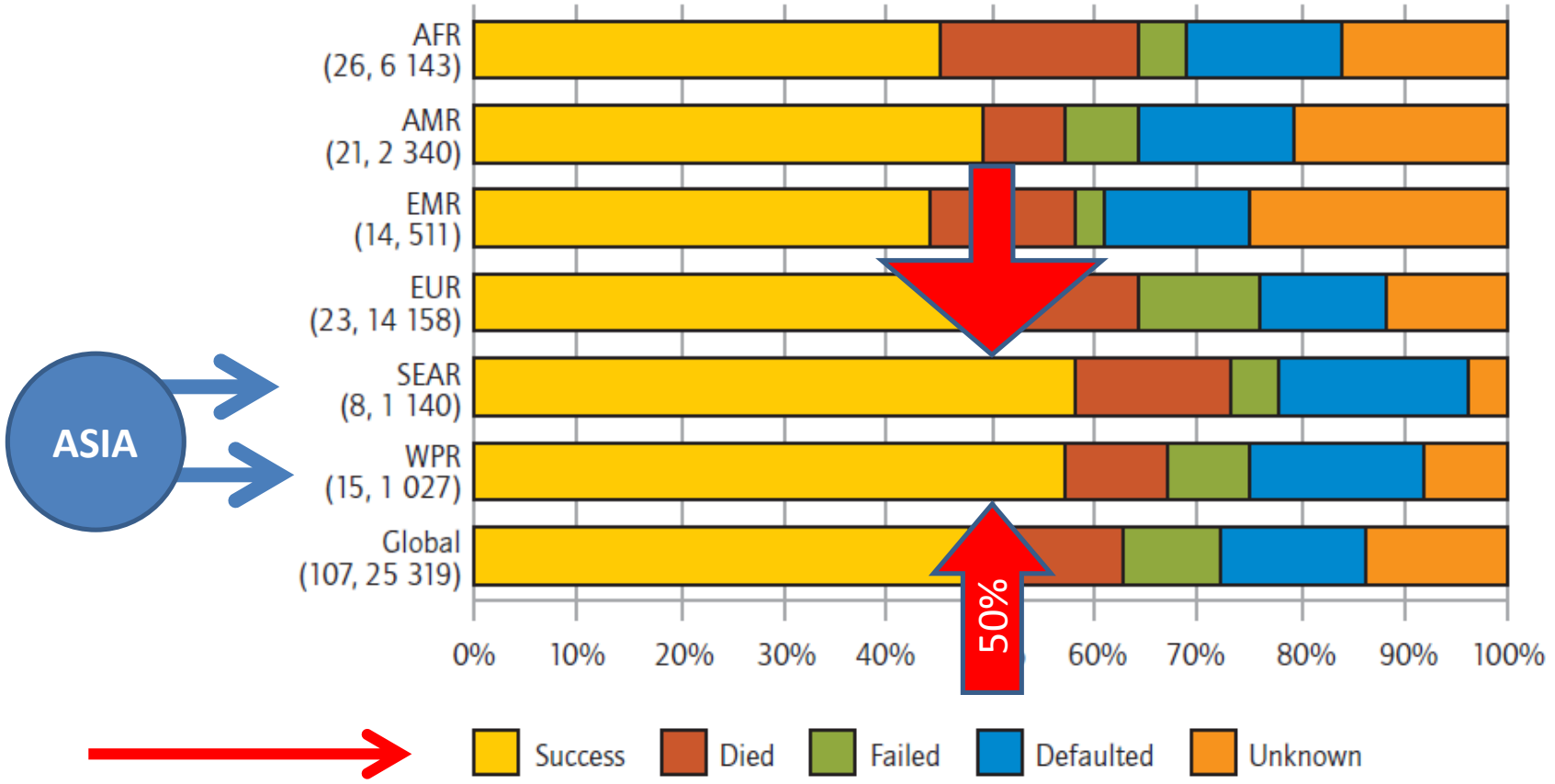
Chang KC et al WHO Group 5 Drugs and Difficult MDR-TB: A Systematic Review with Cohort Analysis and Meta-Analysis Antimcrob Agents Chemother 2013

- **Cohort analysis** with robust Poisson regression models and random-effects **meta-analysis** similarly suggest that **linezolid use significantly increased the probability (95% CI) of favourable outcome by 57% (10%, 124%) and 55% (10%, 121%), respectively.** Defining significant associations by risk ratios >= 12 or =<0.9, **neither cohort analysis nor meta-analysis** demonstrated **any significant add-on benefit** from the use of **other Group 5 drugs** on **outcome of patients treated with linezolid, although *selection bias*** might have underestimated their effects.

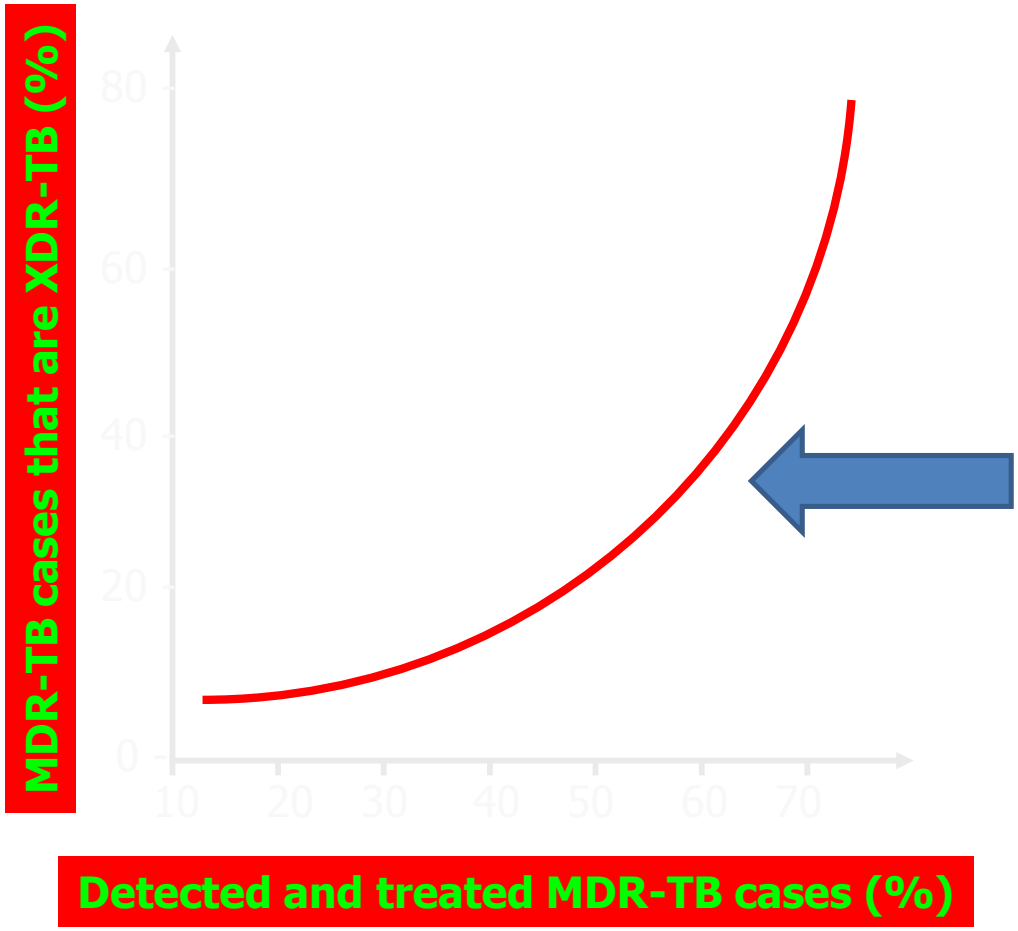
WHO Global TB Report 2012

Treatment outcomes for patients diagnosed with MDR-TB by WHO region, 2009 cohorts.

The number of countries reporting outcomes for at least one case, followed by total cases with outcome data, shown beside each bar.



Blower S et al
Lancet Infect Dis (2007)



"If MDR-TB case detection and treatment rates increase to the WHO target of 70%, without simultaneously increasing MDR-TB cure rates, XDR-TB could increase exponentially. This exponential increase in XDR-TB cases would be the result of synergistic interaction of acquired resistance and transmitted resistance. Under these conditions, i.e. without effective control of MDR-TB epidemics, XDR-TB will quickly become uncontrollable."

Yew WW, Cynamon M, Zhang Y
Emerging Drugs for the Treatment of TB
Expert Opin Emerg Drugs (2011)

There clearly emerges a pressing need to develop

New Anti-TB Drugs **for**

- **Providing shorter, safer, more efficacious and less costly treatment for MDR-TB and XDR-TB**

Important Desirable Characteristics of a NEW Antituberculosis Drug

Yew WW et al Expert Opin Emerg Drugs 2011

Antimicrobial Profile

- Good sterilising activity
  Shortened duration Px (≤4 mo)*; Low relapse rate (≤5%)
- Good bactericidal activity
  High cure rate (≥95%)
- No cross-resistance with current drugs (especially rifampicin and isoniazid)
- Significant postantibiotic effect (preferably ≥12h)
- Narrow antibacterial spectrum
- Potential immunomodulation

Pharmacological Profile

- Good formulation stability under field conditions
- Good oral bioavailability (≥90%)
- Ready delivery by multiple systems / channels
- Absence of drug-drug interactions (both among antituberculosis drugs and others)
- Good lung penetration
- Long elimination half-life (for once-daily or less frequent dosing)
- ? Limited protein binding (preferably ≤50%)

Safety Profile

- No genotoxicity / mutagenicity
- Good clinical tolerance and absence of toxicity

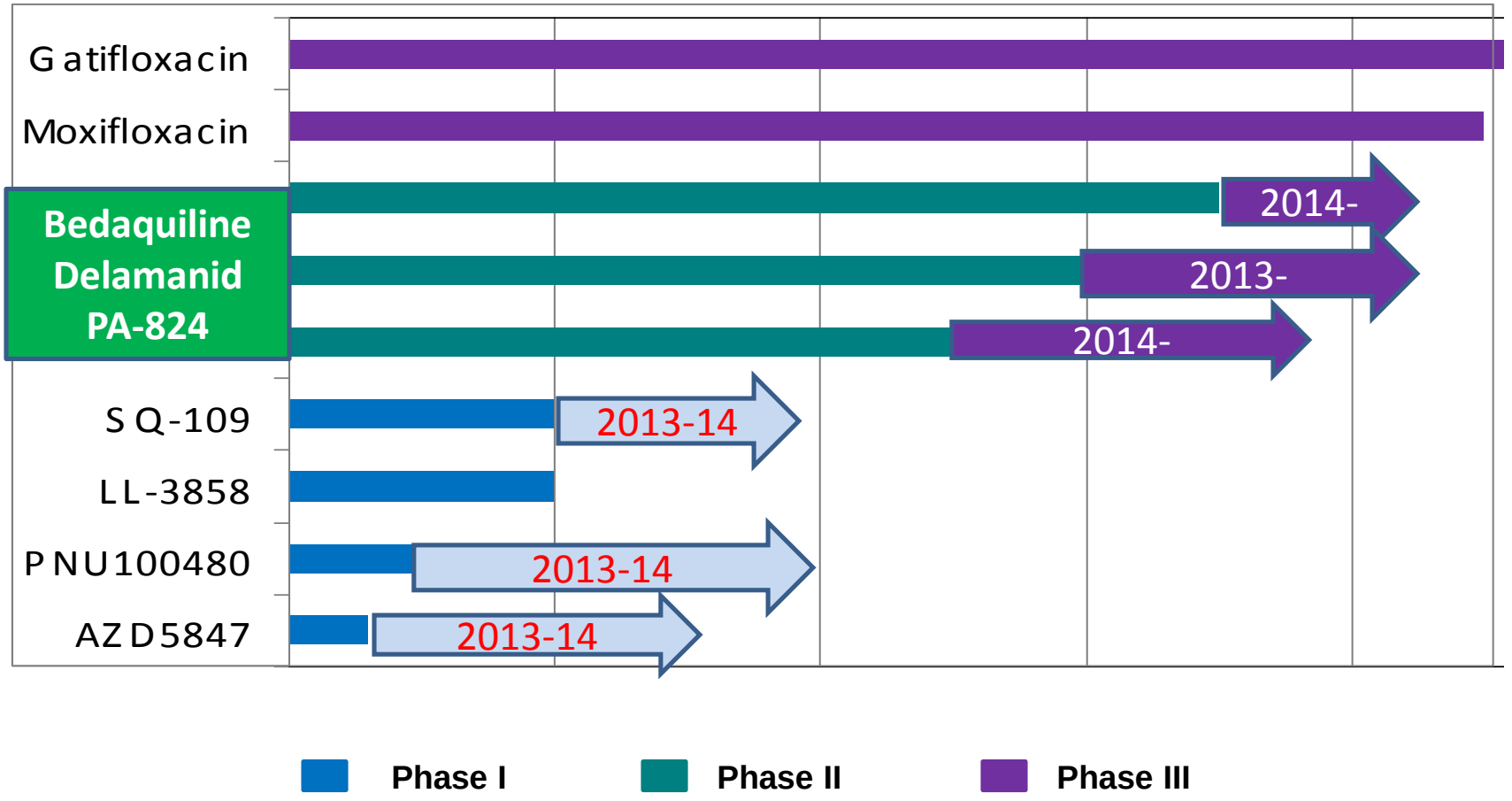
Cost

- Affordable

* ? ≤9 mo for MDR tuberculosis

Nuermberger, Spigelman, Yew
Respirology (2010) Adapted

New Anti-TB Drugs: Global Clinical Portfolio



Diacon AH et al
The Diarylquinoline TMC207 for Multidrug-Resistant TB [1]
N Engl J Med (2009)

- **In the first stage of a 2-stage, phase 2, randomized, controlled trial, 47 patients who had newly diagnosed MDR-TB to receive either TMC207 (400 mg daily for 2 weeks, followed by 200 mg 3X a week for 6 weeks) – 23 patients, or placebo – 24 patients**

- **Addition of TMC207 to standard therapy reduced the time to conversion to a negative sputum culture, as compared with placebo (HR 11.8; 95% CI 2.3 – 61.3, P = 0.003 by Cox Regression Analysis)**

Diacon AH et al
The Diarylquinoline TMC207 for Multidrug-Resistant TB [2]
N Engl J Med (2009)

- **Addition of TMC207 increased the proportion of patients with conversion of sputum culture (48% vs 9%)**

- **The mean log_{10} CFU count in sputum also declined more rapidly in the TMC 207 group than in placebo group**

- **Most adverse events were mild to moderate, and only nausea occurred significantly more frequently among patients in the TMC 207 group than among patients in the placebo group (26% vs 4%, P = 0.04)**

Phase IIb Bedaquiline Study

- **Cause for 5X Increased Rate of Death in Patients Allocated to Receive Bedaquiline?**

PHASE III STUDIES MANDATORY TO CONFIRM SAFETY

Gier MT et al Delamanid for MDR Pulmonary TB N Engl J Med 2012

- RCT: 161 patients received the study drug at a dosage of 100mg BD, 160 patients received the study drug at 200mg BD, and 160 patients had placebo
- Among patients who received a background regimen plus the lower dosage of delamanid, 45.4% had sputum culture conversion compared to 29.6% in the placebo group (P=0.008)
- Likewise, those who had the higher dosage of delamanid had a higher proportion of sputum culture conversion (41.9%, P=0.04)
- Most adverse events were mild to moderate and were evenly distributed in the groups, except for the QT prolongation associated with the study drug use

Yew WW, Nuermberger E. High-Dose fluoroquinolones in Short-Course Regimens for Treatment of MDR-TB: The Way Forward?
Int J Tuberc Lung Dis (2013)

There may be potential pharmacodynamic interaction between high-dose fluoroquinolones and newly developed anti-tuberculosis drugs such as bedaquiline and delamanid, resulting in

additive risk of cardiotoxicity

in some patients

Can We Understand DRUG-Induced Cardiotoxicity Better?

DRUG-INDUCED TOXICITY

DRUG

Parent Compound
Metabolite

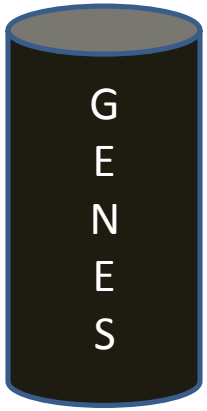
Dose-related

Idiosyncrasy

HOST

Susceptibility

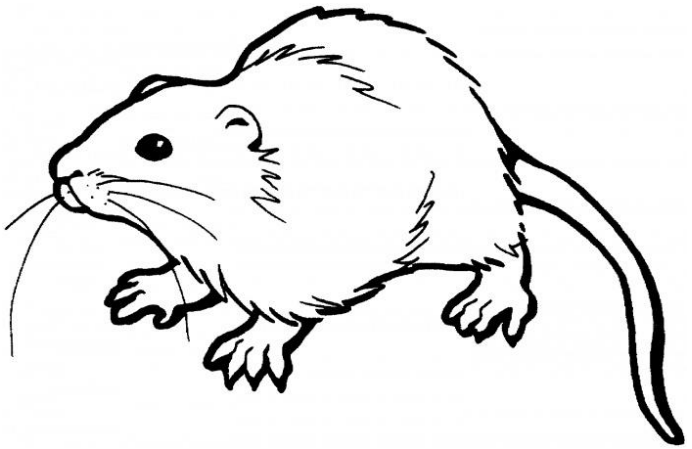
Pathogenesis



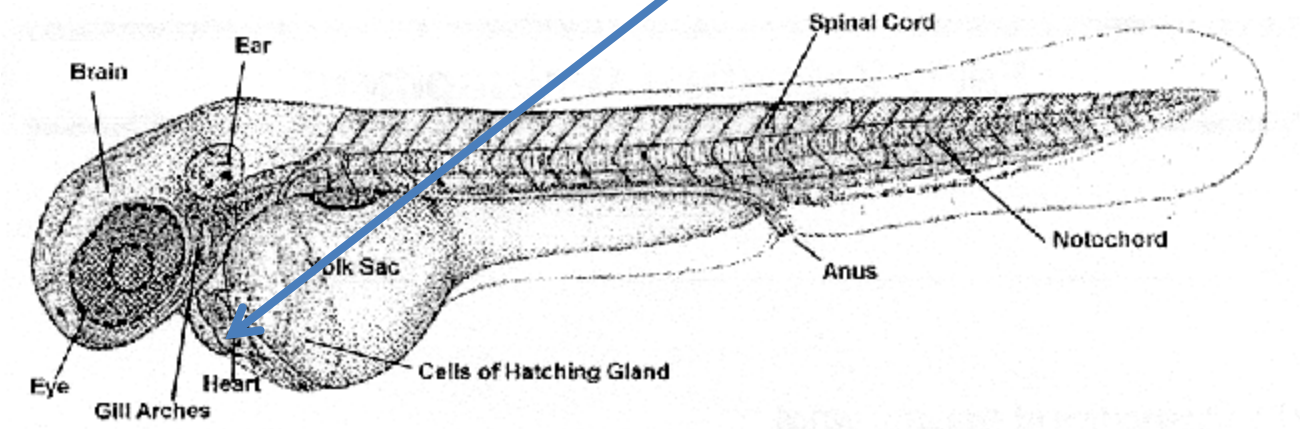
Nishimura Y et al

Genomic Biomarkers for Cardiotoxicity in Rats as a Sensitive Tool in Preclinical Studies

J Appl Toxicol (2013)



Chen J et al Comparative Genomics Identifies Genes Mediating Cardiotoxicity in the Embryonic Zebrafish Heart Physiol Genomics (2008)



Comparison of human and zebrafish protein-coding genes and their orthology relationships

Relationship type	Human	Core relation	Ratio
Data and orthology relationship d (http://www.ensembl.org/inf			
One to one	-		
One to many	3,105		
Many to one	1,247		
Many to many	743		
Orthologous total	14,623		
Unique	5,856	-	
Coding-gene total	20,479	-	26,206

HIV/TB Drug Toxicity Collaborative Research Project (s) With University of Macau

Comparison to the human reference genome shows that approximately 70% of human genes have at least one obvious zebrafish orthologue.

New Paradigms in Drug Development and Prudence in Application

- ……To meet current needs, **new paradigms** in drug development, such as the **"combination" approach** to **shorten the timeline**, is much desired. Thus there is a hope that in the future, drug development would be in a **"per regimen"** basis rather than the conventional " per drug" approach. On top, much care must be exercised to **avoid loss of the new agents through bacillary resistance** developed during use.

- **Diacon AH et al 14-Day Bactericidal Activity of PA-824, Bedaquiline, Pyrazinamide and Moxifloxacin Combinations : A Randomized Trial (Lancet 2012)**

PA-824-Moxifloxacin-PZA is potentially suitable for treatment of drug-sensitive and drug-resistant TB. Multiagent EBA studies can contribute to reducing the time needed to develop new anti-TB regimens

Phase III Study to commence

Potential Problems of (New) Drug Combinations

- ***INTERACTION***

- **Activity against pathogens: Antagonism**

- **Tolerance by patients: Toxicity**

Inhaled Therapy?

- Aminoglycosides
- Other Injectables
- Fluoroquinolones
- Rifamycins

Aims of Inhaled Therapy

- Increase local bioavailability
- Decrease systemic bioavailability

SAFETY OF INHALED THERAPY

While systemic toxicity of the drug may be reduced, local insult to the respiratory tract and pulmonary parenchymal epithelium, by the drug or the conveying vehicle, needs to be fathomed, in terms of possibility of inflammatory response and damage produced in the host organ.

COMPROMISED SYSTEMIC EFFICACY

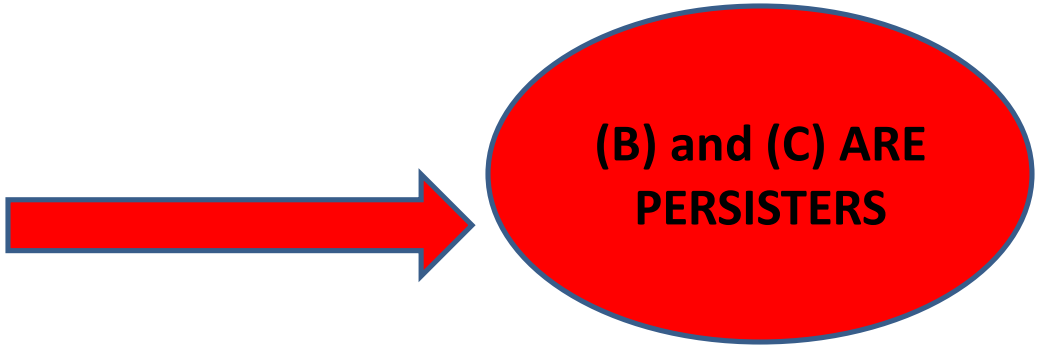
- **Relapse of TB disease can occur from**
- **Intrathoracic sites, such as mediastinal lymph nodes and pleural surfaces**
- **Extrapulmonary organ sites, such as kidney and bones.**

May be a combination of oral and inhaled delivery seems more logical


TB is like a "Russian Doll", consisting of layer after layer of different bacterial populations within a large bacterial population.
Zhang Y. The Magic Bullets and TB Drug Target. Annu Rev Pharmacol Toxicol (2005)

Growth Characteristics of Mtb Populations

- (A) Rapid growth: active
- (B) Intermittent growth: semi-dormant
- (C) Slow growth: semi-dormant
- (D) No growth: dormant



Zhang Y, Yew WW, Barer MR

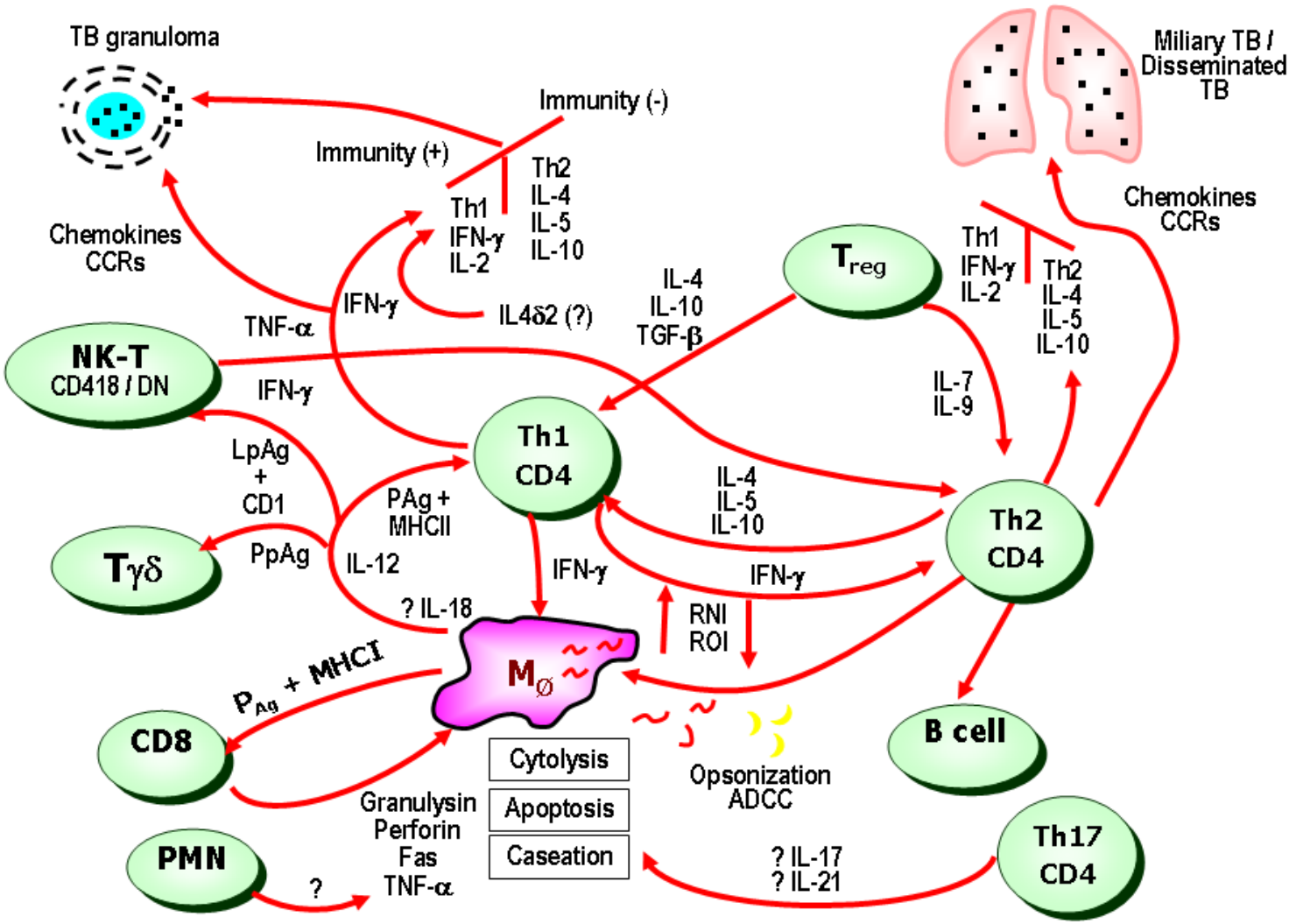
Targeting Persisters for TB Control

Antimicrob Agents Chemother 2012

- Persisters are heterogeneous in nature and comprise varying proportion of the population depending on circumstances…..multiple pathways for formation…….combination of persister-targeted approaches…… drug scheduling, development of new drugs, IMMUNOTHERAPY…… personalized treatment regimens.

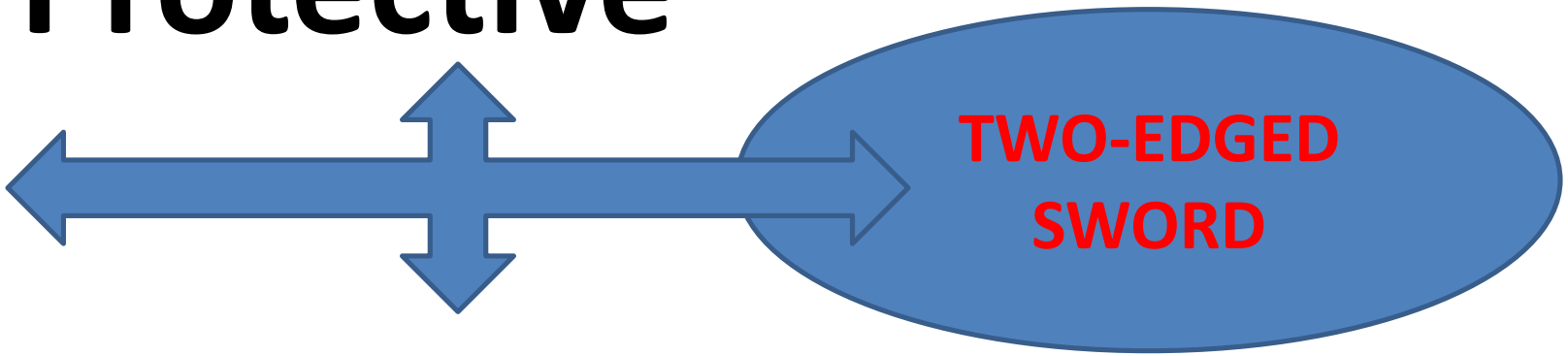
Immunopathogenesis of TB

Yew, Lange, Leung.
Eur Respir J (2010)



Host Immune Response to *Mycobacterium tuberculosis*

- **Protective**



- **Proinflammatory**

Potential Adjunct Cytokine (and Interleukin) Therapy in TB Management?

- Interferon-gamma
- Interleukin-2
- Interleukin-12
- Interleukin-7
- Interleukin-15 (?)
- Interleukin-17 (?)
- Interleukin-18 (?)
- Interleukin-21 (?)
- Interleukin-27 (?)

Some Possible Immunotherapeutic Vaccines/Agents in TB Management?

- **Mycobacterium vaccae: Parenteral/ Oral*
  *V7 Longcom batch, *V7 Immodulon batch**
- **V5 Immunitor**
- **Immunoxel (Dzherelo)**
- **Vitamin D (?)**

In an orchestra, there are many interacting players!

But with the love of life, there is sunrise above the clouds ……